

RESPONSE TO OFFICE ACTION

A. Status of the Claims

Claim 1 has been amended to recite the limitation of previous claim 13. Claim 13 has been canceled in view of this amendment. No subject matter is disclaimed by this amendment. Claims 1, 2, and 4-10 are currently pending in the case and are presented herein for reconsideration.

B. Rejection Under 35 U.S.C. §103

The Action maintains the rejection of claims 1, 2, 4-10 and 13 as obvious under 35 U.S.C. §103(a) over Padgett *et al.* (*Crop Science* 35:1451-1461, 1995) in view of Russell *et al.* (EPO 0430511A1), further in view of Hacker *et al.* (U.S. Patent No. 5,599,769). In particular, it is stated that Padgett *et al.* teach soybean plants having tolerance to glyphosate and Russell *et al.* teach soybean plants having tolerance to glutamine synthetase inhibitors, and that Hacker *et al.* teach herbicidal compounds containing more than one herbicide, including glyphosate and glufosinate, thus providing the motivation to cross the plant of Russell with the plant of Padgett to arrive at the claimed plants.

1. **The First and Second Byrum Declarations Establish Non-Obviousness**

Applicants initially note that claims 1 and 2 have been amended to clarify that the claimed plants and seeds result in a commercially acceptable grain yield. This aspect underscores the non-obviousness of the claimed invention as previously explained in the Declaration of Dr. Joseph R. Byrum submitted with Applicants' previous response. Dr. Byrum explained previously, for example, that a soybean variety had never been developed having more than one herbicide resistance transgene combined in a single soybean plant prior to the current invention. It was also explained that the expression of herbicide resistance transgenes requires

manipulation of complex metabolic pathways of plant cells. As soybean plants do not naturally exhibit herbicide tolerance, the results of a given modification are unpredictable.

Dr. Byrum also explained that transgene expression causes complex pleiotropic effects that may or may not be detectable at the phenotypic level. The effects can vary depending upon factors that include location of insertion of the transgene, the type of transgene being expressed, the genotype of the host soybean plant, and the regulatory elements and any enhancers used to express the transgene. It was further explained that the expression of enzymes not normally present in the plants creates a “metabolic drag” reducing energy from the diversion of resources to the expression of the transgene. Combined with the uncertainty of potential interactions among interrelated metabolic pathways, including negative or positive feedback regulation of different pathways from altered substrate or precursor production, the difficulties are not merely additive when combining multiple herbicide resistance transgenes, but rather are exponential. For example, it was noted that metabolic drag and/or pleiotropic effects associated with transgene expression could have been expected to limit the availability of necessary substrates in the metabolic pathways. It was noted in this regard that certain traits are known to be negatively correlated, such as protein and oil. Dr. Byrum therefore concluded that one of skill in the art simply would have had no reasonable expectation of success as of the priority date that transgenes conferring tolerance to glyphosate and glufosinate could both be properly expressed to obtain the requisite herbicide tolerance.

The current Action nonetheless asserted that this information was not persuasive stating, for instance, that the examples given were not transgenes, and thus doubting that any metabolic drag or other deleterious effect would be expected from stacking transgenes. Applicants are therefore submitting herewith the Second Declaration of Dr. Byrum demonstrating that in fact

one of skill in the art as of the filing date would have been aware of multiple reports of such a metabolic drag which, regardless of ultimate veracity, demonstrate a lack of reasonable expectation of success in arriving at the invention as of the filing date or a motivation for attempting to do so. For example, Dr. Byrum explains that, as of the priority date, one of skill in the art would have been aware of numerous reports asserting the presence of a yield or metabolic drag associated with a transgene conferring glyphosate tolerance. For example, in referring to studies carried out in 1995-1996 with respect to a single glyphosate tolerance transgene, the March 15, 1999 issue of *Soybean Digest*, an industry-recognized magazine, stated that

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This yield lag factor for RR soybeans has been mentioned by many scientists and top-end growers who made side-by-side comparisons since 1996, when these transgenic varieties were first commercialized. And it was mentioned in each of *Soybean Digest's* Special Reports on Herbicide-Tolerant Crops since 1996.

Dr. Byrum also refers to research carried out in 1995-1996 as cited in Raymer *et al.*, 2003 (*Crop Sci.* 43:1584-1589) as follows:

Although yields of some RR cultivars in some trials were often above the mean yield of the trial, seed yields of the population of RR cultivars as a whole averaged 2.9 units below the mean (Fig. 2). In comparison, seed yields of conventional southern regional check cultivars averaged 1.0 unit above the trial mean and 3.9 units higher than the average of all RR entries.

Further cited is a November 1996 newsletter of the University of Missouri Agricultural Experiment Station which states:

Do Roundup Ready Varieties Have the Genetic Ability to Yield as Well as the Top Non-transformed Varieties? This year there was a statistically significant

difference in soybean seed yield between the transformed and non-transformed variety in the test. Untreated Pioneer 9362 yielded 52.8 bushels/acre. Untreated Pioneer 9363RR yielded 46.6 bushels/acre. Since the LSD was 4.6 bushels/acre, the data indicates a statistically higher yield for the non-transformed soybean variety...

In summary, the data generated by this study raise the question of whether there is a "yield drag" with Roundup Ready™ soybeans. In this work, there was some indication that this was the case, but one year's data should not be used to make long term decisions. It does raise a flag that warrants further work in the selection of transformed verses non-transformed crop varieties. It should also provide producers a reason to be cautious about large scale adoption of this weed control system without some personal experience with it in their own operation.

Therefore, one of ordinary skill in the art would not have reasonably predicted as of the filing date that a plant could be obtained comprising transgenes conferring tolerance to glyphosate and glufosinate and also having commercially significant yield. Whether this is true today is completely irrelevant for purposes of the §103 analysis, as whether an art is predictable or whether a proposed modification or combination of the prior art has a reasonable expectation of success is determined at the time the invention was made. See MPEP § 2143.02, *citing Ex parte Erlich*, 3 USPQ2d 1011 (Bd. Pat. App. & Inter. 1986). In this case, it was an open question in the art as of the priority date whether a single transgene could be expressed without deleteriously impacting yield, let alone two such genes.

One of ordinary skill in the art therefore would have also been without any motivation to attempt to arrive at the invention. As explained in the specification, yield is routinely considered the highest priority by most soybean breeders. In fact, Oplinger *et al.*, 1999 (www.biotech-info.net/soybean_performance.pdf) asserted that a 4% yield loss allegedly due to the presence of a glyphosate tolerance gene in RR soybeans would represent a loss to farmers of approximately \$1 billion dollars per year if averaged across the entire U.S. soybean crop. While applicants do not agree with the 4% loss figure, this is evidence of the importance placed on yield in soybeans

and of the general expectations in the art. The allegations of a yield loss for a single transgene would only be expected to be compounded in the case of two such transgenes. One of ordinary skill in the art as of the filing date would therefore have been taught away from attempting to stack multiple herbicide tolerance transgenes, and would not have reasonably believed a commercially significant yield could be obtained when doing so. This evidence therefore fully establishes that the non-obviousness of the claims.

2. Schell *et al.* do not Teach the Desirability of Stacking of Transgenes in Crop Plants

Although the Action cites Schell *et al.*, (1983) to further support that herbicide/antibiotic resistance-gene stacking was possible, this reference in no way teaches that such stacking would be desirable or agronomically useful, especially in a crop plant such as soybean being bred for agronomic quality improvement. No plants with stacked herbicide (or antibiotic) tolerant traits are even apparently described. That is, at best the reference might be relevant to an “obvious to try” rationale. Schell instead describe initial (1983) laboratory-based approaches with petunia, tobacco, carrot and cauliflower cells. Few regenerated plants are even mentioned, and no effects of transformation on their agronomic traits, in a field or even a greenhouse, are discussed. In fact, it is not even shown that the genes are herbicide tolerance transgenes rather than antibiotic marker genes. Further, all of the plants, if they are crop plants at all, are ones that were grown for harvest of vegetative tissues and these are not shown to have any relevance to soybeans. None of these described plants are routinely grown for grain (seed) yield, and one of skill in the art would realize that effects on vegetative yields and seed yields are not correlative, especially if it were the case that reproductive tissues are more sensitive to the action of a herbicide than are vegetative tissues. The reference therefore in no way supports the rejection.

3. Russell *et al.* Does Not Describe Fully Transgenic Glufosinate Tolerant Soybean Plants

Applicants note that Russell *et al.* specifically state that the soybean shoots produced from their described research and grafted onto non-transgenic root stocks were presumed to be chimeric (see, *e.g.*, paragraphs [0027], [0042] of Russell *et al.*). No germline transformation was described, nor any fully transgenic plants. The chimeric shoots were not tested for any agronomic qualities such as seed yield. Following grafting, no further growth in the presence of glufosinate is actually described. Indeed, it is unclear that the progeny of plants produced by the methods of Russell *et al.* would even be transgenic or glufosinate tolerant. The present Action (and the preceding Action) mistakenly asserts that Russell *et al.* teach “soybean plants that have resistance to glutamine synthetase inhibitor via transformation” (September 26, 2005 Action, page 7). Thus, the teachings of Russell *et al.* do not properly provide one of skill in the art with either the motivation or the tools to create soybean plants comprising stacked transgenes that convey glyphosate and glufosinate tolerance. One of skill in the art simply could not have been expected to combine the Russell and Padgett references to arrive at the present invention.

4. Hacker *et al.* Teaches Away from the Invention

The Hacker *et al.* reference (U.S. 5,599,769, issued Feb. 4, 1997) is said to teach use of multiple herbicides to obtain a synergistic effect and thereby allegedly motivate those of skill in the art to combine genes conferring tolerance to these herbicides. However, Applicants respectfully submit that the reference if anything teaches away from the invention, and expressly demonstrates the lack of any motivation in the art to arrive at the invention. For example, the position in the Action is apparently that Hacker *et al.* provide a motivation to arrive at the invention because one of skill in the art would seek to take advantage of an increased synergistic

herbicidal activity by stacking genes conferring glyphosate and glufosinate tolerance and treating the plant with a mixture of these herbicides.

The Action states in this regard, for example, that Hacker show that “when applied in combination the active substance is much more efficient than when applied individually” and that “[h]aving crops comprising genes conferring resistance to both glyphosate and glufosinate allow to apply herbicide combination [sic] and thus to obtain a better control of weeds.” Finally, it is stated that “[t]he combination of glyphosate and glufosinate is synergic hence; this combination achieves an effect of which each is incapable.” See Action at p. 4, 1st ¶. Thus the very basis for the assertion of a motivation to combine in the art is the fact that the herbicidal activity of glyphosate and glufosinate is *not additive* and is *unpredictable* relative to each herbicide activity alone.

The Hacker reference therefore if anything teaches away from the invention and expressly demonstrates the lack of any reasonable expectation of success in the art. Hacker *et al.* specifically shows that the herbicidal activity of glyphosate *or* glufosinate alone does not correlate to what would be expected for the combination of glyphosate *and* glufosinate, *e.g.*, they are not additive. This also indicates that the ability to confer herbicide tolerance to glyphosate *or* glufosinate alone is not predictive of tolerance to the combination of glyphosate *and* glufosinate. One of skill in the art would therefore have been without any reasonable expectation that any benefit could be obtained by attempting to prepare a plant comprising transgenes conferring tolerance to glyphosate and glufosinate. At best it would be “obvious to try” absent application of impermissible hindsight reconstruction, with no evidence found anywhere on the record or in the art suggesting that success could at all be predicted. In fact, the synergistic activity described by Hacker *et al.* would lead one to believe that success would *not* be obtained. Such

unpredictability is the epitome of nonobviousness, as it is specifically the burden of the Office to show the expectation of success and motivation to combine on the record by substantial evidence. *In re Rinehart*, 531 F.2d 1048, 189 USPQ 143 (CCPA 1976); *In re Gartside*, 203 F.3d 1305 (Fed. Cir. 2000). Withdrawal of the rejection is thus respectfully requested.

5. Summary

In sum, Applicants have affirmatively presented substantial evidence demonstrating that, as of the priority date, one of skill in the art would not have had a motivation or reasonable expectation of success in producing a soybean plant comprising transgenes conferring glyphosate and glufosinate tolerance and having a commercially significant yield, both from the standpoint of herbicide tolerance and yield. Applicants reiterate that regardless of the description of soybean plants resistant to glyphosate or glufosinate alone, the fact remains that prior to the invention one of skill in the art would not have known how multiple herbicide tolerance genes would interact. This is underscored, as shown by declaratory evidence on the record, by the unpredictable and synergistic effects observed when herbicides are combined, the complex biochemical pathways that must be modified to obtain herbicide tolerance, the state of teaching in the art and the unpredictable and non-additive manner in which genes interact in plants as noted in the specification and Declaration of Joseph Byrum. The Second Declaration of Joseph Byrum further demonstrates that at the priority date one of skill in the art would have had no clear motivation to combine such transgenes, and no reasonable expectation that such a combination would lead to a desirable result from the standpoint of seed yield.

Applicants therefore respectfully submit that nonobviousness has been fully established on the record by substantial evidence and that no evidence has been presented for doubting this showing. Removal of the rejection under 35 U.S.C. § 103 is thus respectfully requested.

C. **Conclusion**

In light of the foregoing, applicants submit that all claims are in condition for allowance, and an early indication to that effect is earnestly solicited. The examiner is invited to contact the undersigned (512)536-3085 with any questions, comments or suggestions relating to the referenced patent application.

Respectfully submitted,



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